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Cost-effectiveness analysis of the introduction of rotavirus vaccine in Iran

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ABSTRACT

Background: Although the mortality from diarrheal diseases has been decreasing dramatically in Iran, it still represents an important proportion of disease burden in children <5 years old. Rotavirus vaccines are among the most effective strategies against diarrheal diseases in specific epidemiological conditions. This study aimed to evaluate the cost-effectiveness of the introduction of rotavirus vaccine (3 doses of pentavalent RotaTeq® (RV5)) in Iran, from the viewpoints of Iran's health system and society.
Methods: The TRIVAC decision support model was used to calculate total incremental costs, life years (LYs) gained, and disability-adjusted life years (DALYs) averted due to the vaccination program. Necessary input data were collected from the most valid accessible sources as well as a systematic review and meta-analysis on epidemiological studies. We used WHO guidelines to estimate vaccination cost. An annual discount rate of 3% was considered for both health gain and costs. A deterministic sensitivity analysis was performed for testing the robustness of the models results.
Results: Our results indicated that total DALYs potentially lost due to rotavirus diarrhea within 10 years would be 138,161, of which 76,591 could be prevented by rotavirus vaccine. The total vaccination cost for 10 cohorts was estimated to be US$ 499.91 million. Also, US$ 470.61 million would be saved because of preventing outpatient visits and inpatient admissions (cost-saving from the society perspective). We estimated a cost per DALY averted of US$ 2868 for RV5 vaccination, which corresponds to a highly cost-effective strategy from the government perspective. In the sensitivity analysis, all scenarios tested were still cost-saving or highly cost-effective from the society perspective, except in the least favorable scenario and low vaccine efficacy and disease incidence scenario.

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Conclusion: Based on the findings, introduction of rotavirus vaccine is a highly cost-effective strategy from the government perspective. Introducing the vaccine to the national immunization program is an efficient use of available funds to reduce child mortality and morbidity in Iran.

1. Introduction

The high prevalence and incidence of diarrhea are recognized as a major health problem. There were nearly 1.7 billion diarrhea episodes among children less than 5 years of age in low- and middle-income countries in 2010 [1]. Diarrheal disease is also the second leading cause of death in children under 5 years old, killing about one million children every year [2].

Rotavirus is the most important cause of severe diarrhea in infants and young children worldwide [3,4]. Rotaviruses are ubiquitous, and 95% of children are infected by the age of 5 years. Rotavirus is responsible for a large proportion of the above-mentioned deaths and 20–54% of acute diarrhea episodes worldwide [5–7].

Eesteghamati and his colleagues [8] reported that rotavirus is the most important cause of severe diarrhea among hospitalized children aged less than 5 years old in Iran. Those researchers also found that rotavirus disease accounts for more than one-half of all hospitalizations for severe diarrhea.

Recent studies show that rotavirus vaccines might be the best choice for preventing severe rotavirus disease and the deadly dehydrating diarrhea that it causes, particularly in low-income countries where access to treatment for RV is limited [9,10]. There are two rotavirus vaccines: the pentavalent RotaTeq® (RV5) (Merck and Co. Inc., West Point, Pennsylvania, USA) and the monovalent Rotarix® (RV1) (GlaxoSmithKline Biologicals, Rixensart, Belgium). Studies of the rotavirus vaccine have shown that the efficacy of RV5 and RV1, respectively, against rotavirus gastroenteritis of any severity was 74.0% (95% confidence interval (CI) 66.8–79.9) and 87% (95% CI 79.6–92.1) [11,12]. More importantly, the rotavirus vaccines can prevent approximately 98% of severe infections and 70% to 100% of emergency department visits and hospitalizations from rotavirus [12–14].

Decisions to adopt vaccination programs depend on multiple factors, including the disease prevalence and incidence, vaccine efficacy, and cost-effectiveness of a vaccination program. Although some studies have estimated the cost-effectiveness of rotavirus vaccination [15–18], most of them have been conducted in developed countries, not in developing nations. Results of cost-effectiveness studies can vary among countries due to differences in epidemiological patterns, patients' characteristics or health system variables (such as incidence/prevalence of disease, adherence to the treatment regimen, individuals' preferences for particular levels of health, unit costs of inputs into health care, and variation in how health care is delivered). Moreover, no simple rule is available to indicate how the results of cost-effectiveness studies in developed countries might translate to health care delivery settings in developing nations.

The major serotype of rotavirus in Iran is G4P [8] and other dominant strains are P [8] with G nontypeable, G4 with P nontypeable, G1 [P8], and G2 [P4] [8]. Although the major serotype can be covered by RV1 through cross-reactivity, RV5 provides direct protection against it. Also, based on a recent systematic review, RV5 was used in the unique study that reported vaccine efficacy against G4 and P [8] in middle-income countries [19]. Therefore, we conducted this study to evaluate the cost-effectiveness of RV5 vaccination compared to no vaccination in Iran.

2. Methods

2.1. Study design

This economic evaluation was conducted from the perspectives of Iran's government and its society; in the governmental perspective, those direct medical costs imposed on governmental health system were included and in the societal perspective, all direct medical costs that imposed on society including (patients' families or government) were included. The TRIVAC model, a decision-support model developed by the ProVac Initiative of the Pan American Health Organization (PAHO) in collaboration with the London School of Hygiene and Tropical Medicine (LSHTM) [20], was used to calculate total incremental costs, life years gained, disability adjusted life years (DALYs) averted due to the vaccination program, and an incremental cost-effectiveness ratio (ICER). A data collection procedure was used in order to obtain the necessary input data from the most valid accessible sources for the analysis.

We used the assumptions made by TRIVAC for the natural history of rotavirus. We classified rotavirus as non-severe or severe cases of rotavirus gastroenteritis (RVGE). TRIVAC is a static model that only crudely takes account of the indirect protection of the vaccination on unvaccinated children through herd immunity or of the negative effects of type replacement. A crude multiplier of direct vaccine efficacy can be applied to replicate a herd effect; also, vaccine efficacy can be decreased to reflect the circulating serotypes [20]. We assumed 2014 as the year of introduction of the vaccine and included children 1–59 months old for 10 sequential birth cohorts in the analysis (2014–2023). The time horizon for health and economic benefits has been defined in the TRIVAC model specifications [20]. An annual discount rate of 3% was considered for both health gain and costs.

2.2. Input epidemiological and effectiveness data

2.2.1. Demographic data

The number of live births was derived using data from Iran's National Organization for Civil Registration. We used the last Multiple-Indicator Demographic and Health Survey (IrMIDHS, 2010) to obtain mortality rates among children [21]. We also used the United Nations Population Division database to extract the estimates for current life expectancy of women and men in Iran and also estimates for the future [22].

2.2.2. Disease burden

An epidemiologic model was used to estimate the incidence of diarrheal diseases. According to the 2010 Demographic and Health Survey (DHS) report [21], the 14-day prevalence of all-cause diarrhea was 13.5% in Iran (the IrMIDHS study was performed between 22 December 2010 and 20 January 2011). This included all children who had a new episode of diarrhea within 14 days before survey or those whose episode started before the period, but still were symptomatic during the period. All cases of diarrhea started within (duration-1) days before the first day of study period, were among the prevalent cases at least in the first day of the period. We used the pooled estimate for the weighted median of duration of diarrhea in low- and middle-income countries for children 0–59 month old, which was 3.1 days (3.0–3.2) in a systematic review

[23]. We rounded it to 3 days for calculation purposes. Considering a 3-day duration for all-cause diarrheal diseases, the daily incidence rate was estimated 8.4 per 1000 person-day based on the $I = PP/[\text{study period} + (D - 1)]$ formula, where I, PP and D indicate incidence, period prevalence and duration, respectively. Assuming no systematic difference between the study period and whole calendar year, annual incidence rate of all-cause diarrhea was estimated to be 307,968 episodes per 100,000 children.

To estimate the proportion of rotavirus diarrhea from all-cause diarrhea, we used the results of a systematic review and meta-analysis [24]. That review included all Iranian studies indexed in the international and national databases, including PubMed, Ovid Medline, Science Direct, Google Scholar, Institute for Scientific Information (ISI), and Scopus as well as Iran Medex and Irandoc for Farsi-language papers [25]. The systematic review included 21 studies on hospital cases from 11 different provinces (10,997 cases) and 15 studies on outpatient cases from 7 different provinces (4371 cases). For hospital and outpatient settings, the pooled estimates with random effect were 39% (95% CI: 32–47%) and 31% (95% CI: 23–38%), respectively. Based on the opinion of clinical expert in the research team, in our model we used the pooled estimate of the outpatient setting (31%) as the percentage of all-cause diarrhea incidence that is attributable to rotavirus. That is because the incidence in community was the parameter of interest in the model, rather than hospitalizations.

We estimated the number of deaths attributed to rotavirus diarrhea based on statistics from the national registry of childhood deaths. Their database reports cause-specific mortality for children <5 years old, with nationwide coverage. For our estimate, we multiplied the proportion of severe cases of diarrheal disease that are due to rotavirus (39%) by the total number of deaths due to diarrheal diseases extracted from that national registry. The disability weight for diarrhea episodes was considered to be 0.119, as used in the model and the 1st global burden of disease (GBD) study. There are updated disability weights for diarrheal diseases [26], but we did not use them, so that our results would be comparable with the results of other local and international studies. The age distribution of disease cases was obtained from an Iranian study on sentinel sites for rotavirus surveillance [8].

2.2.3. Vaccine coverage and efficacy

We assumed that the new vaccine would be administered jointly with another vaccine in the routine schedule [27] (DTP vaccine at 2, 4, and 6 months), with a coverage of 99% and a maximum achievable coverage of 99.5%. Ministry of Health collects administrative data from all rural health houses and urban health posts which are responsible for routine immunization. Those information have good consistency with nationally representative surveys [21]. The vaccination coverage of DTP3 and Hepatitis-B3 are around 99% based on estimates of the Ministry. The rotavirus vaccine efficacy (VE) has not been reported for Iran. Therefore, three scenarios were modeled in order to explore how different scenarios of vaccine efficacy would impact the cost-effectiveness profile in Iran, based on evidence from countries in the same WHO mortality stratum, B (low adult and low children mortality). The first scenario, which was the base-case scenario, incorporated estimates of three-dose VE of 82.2% (70.0–90.1%) against Vesikari scale ≥11 (severe) rotavirus gastroenteritis (RVGE), based on a multi-country study in Latin America [28]. The second scenario used full dose efficacy estimates from Vietnam of 63.9% (7.6–90.9%) against severe RVGE. We also used a very low estimate of VE from the same study (48.3%) in our sensitivity analysis; that was an overall estimate for Vietnam and Bangladesh (WHO mortality stratum B and D, respectively) which is a pessimistic estimate for Iran condition. [29]. The third scenario used efficacy estimates from the Linhares et al. Latin American study against very severe RVGE (Vesikari scale ≥19) of 97.3% (83.8–99.9%) [28]. While RV1 was used in this study instead of RV5, immunogenicity and efficacy estimates for the two vaccines are similar across a range of countries [30]. Partial schedule efficacy, that is, efficacy of only one or two doses (which has been estimated to take into account drop-outs and children who do not receive their full schedule), was calculated according to published studies of Latin America and Asia [28,29]. Efficacy for 1 and 2 doses was equal to 52% and 71% of full doses, respectively. The ratio of VE of non-severe (all who need medical attention except admitted) versus severe cases (admitted) was estimated at 83%, based on the Vesikari et al. study [11]. The relative coverage of deaths was considered to be 90%. This is an adjustment that accounts for a concentration of deaths in the children who are not reached by vaccination—and so the true effectiveness may be lower than the equal distribution of deaths [31]. The annual decrease in dose efficacy, which was used to simulate waning protection, was considered to be 4.8% [28]. In the base-case analysis we assumed no herd immunity exist. We tested a 110% multiplier for VE in sensitivity analysis to estimate the impact of herd immunity. The serotype coverage of RV5 was considered 100% based on frequency of common serotypes in Iran [8] and cross-reactivity; in sensitivity analysis, a 52.7% serotype coverage was tested as low serotype coverage.

2.3. Cost estimation

2.3.1. Vaccination program costs

We used WHO guidelines [32] to estimate the incremental cost of introducing the rotavirus vaccine into the current national vaccination system. The cost of vaccine supplies was calculated using the formula of $C = P \times I \times B \times D \times (1/(1 - w))$, where P is the vaccine price per dose, I is the immunization coverage rate, B is the birth cohort population, D is the number of doses per fully immunized child, and w is the wastage rate.

The price of each dose (US$ 10) was obtained from the local representative of the vaccine's manufacturer. A Ministry of Health representative provided the company with the number of required vaccine doses and officially asked about and negotiated on the price. Finally, we received a pro forma for the vaccine price. The number of doses per child fully immunized for rotavirus was considered as three, and the wastage rate was assumed to be 5%. To estimate the incremental system cost per dose, we included the cost of distribution system, cold chain, surveillance monitoring, training, maintenance, personnel expenses, and the required facilities that are needed beyond the currently available facilities of Iran's Ministry of Health. The total annualized capital cost was estimated based on equipment prices and their useful life and an annualizing factor. In addition, health care personnel costs (all heath care workers involved in this program, including vaccinators) were assessed on the basis of exclusive time allocations for this vaccine and other incentive payment.

2.3.2. Health service utilization and costs

To estimate the total outpatient health care utilization costs, we extracted data on health care seeking during an episode of childhood diarrhea from a representative nationwide study on 14,625 children with diarrheal diseases [33]. The study showed that 70% of cases had at least one visit with a health care provider. Those included visits with a physician in 61.6% of cases and with either a *behvarz* (rural health care worker) or a health post officer (non-physician care provider in urban area) in 8.4% of cases. The rest of the cases (30%) had not had a visit with any health care provider. The personnel cost for physicians was estimated based on a weighted mean of the official price of outpatient visits of general practitioners and specialists in private and public sectors.

We estimated the pattern of prescribing diagnostic tests and medications in severe and non-severe cases by interviewing a wide

Table 1
Input parameters for estimating disease burden.

Parameter	Estimate	Scenarios		Source (s)
		Low	High	
Annual incidence per 100,000 aged 1–59 mo				
Rotavirus (non-severe) cases	92,315	68,492	113,160	[21,36]
Rotavirus (severe) cases	2864	2125	3511	[21,36]
% Case fatality ratios (CFRs) in ages 1–59 mo[a]				
Rotavirus (severe) cases	0.02%	0.01%	0.03%	Child mortality surveillance system of Iran
Disability weight for DALY calculations				
Rotavirus (non-severe) cases	0.119	–	–	[26]
Rotavirus (severe) cases	0.119	–	–	[26]
Mean duration of illness (in days)				
Rotavirus (non-severe) cases	6	–	–	Assumption
Rotavirus (severe) cases	6	–	–	Assumption
Age distribution of disease cases and deaths				
<3 mo	2.4%	–	–	[8]
3–5 mo	7.8%	–	–	[8]
6–8 mo	20.0%	–	–	[8]
9–11 mo	20.0%	–	–	[8]
12–23 mo	35.0%	–	–	[8]
24–35 mo	5.0%	–	–	[8]
36–47 mo	5.0%	–	–	[8]
48–59 mo	4.8%	–	–	[8]

[a] In the absence of vaccination, CFRs are assumed to decline in each successive birth cohort in line with the general trend in under-5 mortality. This is done by assuming the fraction of under-5 deaths caused by the disease remains fixed over time.

range of health professionals, including general practitioners, pediatric assistants, and pediatricians, in the public and private sectors. The average cost of each inpatient episode was estimated based on medical records of 60 patients who were hospitalized for viral diarrhea (based on ICD-10-CM Diagnosis Code A08) in the Mofid Children's Hospital, in Tehran, Iran, in 2012 (average length of stay was 3.1 days and mean age was 2.3 years). All costs were estimated using 2013 price levels or were inflated from previous years to 2013 values using the health sector pay and prices index when appropriate. To have an international perspective all costs were converted from Iranian Rials [IRR] into United State dollars (US$) at an official 2013 currency exchange rate of 24,000 IRR per US$ 1.00 [34].

2.4. Cost-effectiveness measures and sensitivity analysis

The incremental cost-effectiveness ratio (ICER) of vaccination versus no vaccination in the base-case scenario was defined in terms of the ratio of the difference in costs to the difference in effect measures ((vaccine cost – cost saving)/DALY averted).

We also defined our threshold (ceiling rate) for labeling an intervention as being cost-effective or not based on WHO guideline [35]. We conducted a series of deterministic sensitivity analyses to detect those parameters that had the most impact on the ICER, with different input parameters being changed in a sequence to the upper and lower limit, while the other variables were held constant.

Table 2
Input parameters for estimating health service utilization and costs (all costs are presented in 2013 US$).

Parameter	Estimate	Scenarios		Source (s)
		Low	High	
Outpatient visits				
Outpatient visits per disease episode				
Rotavirus (non-severe) cases	0.70	0.50	0.90	[33,36]
Rotavirus (severe) cases	1.00	0.70	1.30	[33,36]
Government cost per outpatient visit[a]				
Rotavirus (non-severe) cases	$2.23	$2.01	$2.45	Calculated
Rotavirus (severe) cases	$4.69	$4.22	$5.16	Calculated
Household cost per outpatient visit[b]				
Rotavirus (non-severe) cases	$3.85	$3.47	$4.24	Calculated
Rotavirus (severe) cases	$6.60	$5.94	$7.26	Calculated
Inpatient admissions				
Inpatient admissions per disease episode				
Rotavirus (severe) cases	0.90	0.80	1.00	[33,36]
Government cost per inpatient admission[c]				
Rotavirus (severe) cases	$174.52	$157.06	$191.97	Calculated
Household cost per inpatient admission[d]				
Rotavirus (severe) cases	$45.29	$40.76	$49.82	Calculated

[a] Government costs per outpatient visit include visit, medications, and diagnostic tests. Outpatient visits in cases who seek medical attention (70%) are distributed as follows: specialist physician (public: 8%, private: 41%), general practitioner (public: 17%, private: 22%), health post officers: 4% and *behvarz* personnel: 8%. The cost presented is the weighted average of the provider-specific costs.

[b] Household costs per outpatient visit include direct medical cost (out-of-pocket payments for consultations and drugs). Outpatient visits in cases who seek medical attention (70%) are distributed as follows: specialist physician (public: 8%, private: 41%), general practitioner (public: 17%, private: 22%), health post officers: 4% and *behvarz* personnel: 8%. The cost presented is the weighted average of the provider-specific costs.

[c] Government costs per inpatient admission include direct medical cost [the cost per bed day multiplied by the expected length of stay (3.1 days) and the cost of any disease-specific drugs and diagnostics]. Inpatient admissions are distributed as follows: 4.8% Social Security hospital, 5.2% private hospitals, and 90.0% public hospitals. The cost presented is the weighted average of the provider-specific costs.

[d] Household costs per inpatient admission include out-of-pocket expenditure for medical cost of medication, hospital care, and diagnostics. Inpatient admissions are distributed as follows: 4.8% social security hospital, 5.2% private hospitals, and 90.0% public hospitals. The cost presented is the weighted average of the provider-specific costs.

Table 3
Input parameters for estimating rotavirus vaccine (RV) coverage and timeliness.

Parameter	Estimate (%)	Scenarios		Source(s)
		Low	High	
Coverage of DTP1 by age in year 2014 (proxy for RV doses given with DTP1)				
3 mo	96.2	–	–	EPI & [37]
6 mo	97.5	–	–	EPI & [37]
9 mo	97.9	–	–	EPI & [37]
12 mo	98.3	–	–	EPI & [37]
24 mo	99.0	–	–	EPI & [37]
Coverage of DTP2 by age in year 2014 (proxy for RV doses given with DTP2)				
3 mo	0.0	–	–	EPI & [37]
6 mo	97.4	–	–	EPI & [37]
9 mo	97.6	–	–	EPI & [37]
12 mo	98.1	–	–	EPI & [37]
24 mo	99.0	–	–	EPI & [37]
Coverage of DTP3 by age in year 2014 (proxy for RV doses given with DTP3)				
3 mo	0.0	–	–	EPI & [37]
6 mo	97.0	–	–	EPI & [37]
9 mo	97.5	–	–	EPI & [37]
12 mo	98.0	–	–	EPI & [37]
24 mo	99.0	–	–	EPI & [37]

Coverage projections over the 2014–2023 period were estimated by assuming RV will achieve the same coverage and timeliness as DTP and by assuming a 5% annual decrease in the gap between final coverage in the cohort (coverage by age 24 mo) and a ceiling of 100% (DTP1), 100% (DTP2), and 100% (DTP3).

Table 4
Input parameters for estimating RV5 program costs.

Parameter	Estimate	Scenarios		Source(s)
		Low	High	
Vaccine dose price projection				
2014	$10.00	$7.00	$12.00	Local representative of the manufacturer
2015	$10.00	$7.00	$12.00	Assumption
2016	$10.00	$7.00	$12.00	Assumption
2017	$10.00	$7.00	$12.00	Assumption
2018	$10.00	$7.00	$12.00	Assumption
2019	$10.00	$7.00	$12.00	Assumption
2020	$10.00	$7.00	$12.00	Assumption
2021	$10.00	$7.00	$12.00	Assumption
2022	$10.00	$7.00	$12.00	Assumption
2023	$10.00	$7.00	$12.00	Assumption
Other vaccine dose costs				
International handling (% of vaccine price)[a]	3.00%	1.00%	5.00%	Assumption
International delivery (% of vaccine price)[b]	2.00%	1.00%	3.00%	Assumption
Wastage (% of doses discarded etc.)[c]	5.00%	3.00%	7.00%	Assumption
Incremental system costs of introduction[d]				
Incremental system cost per dose	$1.13	$1.02	$1.24	Calculated

[a] The handling percentage refers to the international service charges (documents, airports).
[b] Delivery percentage refers to the international shipping cost (international freight), which includes insurance.
[c] The percentage of wastage is converted into a factor [1/(1 − % wastage)] that is multiplied by the expected number of doses required to meet the anticipated level of coverage.
[d] Estimated incremental system costs include cost of personnel (88.4% of cost), training material (8.6% of cost), vehicles and transport (1.7% of cost), and cold chain (1.3% of cost). They are assumed to be recurrent costs each year.

3. Results

Input parameters for estimating disease burden, disease-related service utilization and costs, vaccine coverage, vaccination program costs, and vaccine efficacy are summarized in Tables 1–5. The model's results for outcomes and costs for 10 cohorts from 2014 to 2023 for the entire country are presented below.

3.1. Effectiveness measures

As shown in Table 6, without a vaccination program, there would be 64,464,813 cases of diarrhea over 10 birth cohorts from 2014 to 2023, including 62,524,950 non-severe cases and 1939,863 severe cases. In contrast, with a vaccination program, 35,129,919 cases of diarrhea could be averted. During this period of time, 266 deaths could also be avoided via the vaccination program. Life years gained through vaccination were estimated 7888. Without vaccination, total DALYs lost due to mortality and morbidity from rotavirus diarrhea would be 138,161, while vaccination could prevent 76,591 of them in the same period (Table 6).

3.2. Cost and health care utilization measures

From a societal perspective, our results revealed that within the modeling time horizon, without vaccination there would be 45,125,369 outpatient visits, of which 24,590,943 could be averted via vaccination (Table 6). In addition, the total estimated number of inpatient admissions without vaccination would be 1745,877; 65% of them (1139,256) could be avoided through vaccination. Based on the average cost of each outpatient visit, the total cost of outpatient visits would be US$ 402.08 million without vaccination. Furthermore, the total estimated cost of inpatient admissions would be US$ 383.76 million. Our results show that about US$ 470.6 million would be saved by preventing outpatient visits and inpatient

Table 5
Input parameters for estimating the health impact of RV5.

Parameter	Estimate (%)	Scenarios		Source(s)
		Low (%)	High (%)	
Vaccine efficacy vs non-severe RVGE				
Dose 1	35.4	19.2	42.6	[11,38]
Dose 2	35.4	35.4	42.6	[11,38]
Dose 3	68.1	37.1	68.1	[11,38]
Vaccine efficacy vs severe RVGE				
Dose 1	42.7	41.0	44.1	[28,39]
Dose 2	42.7	42.7	89.4	[28,39]
Dose 3	82.1	63.9	97.0	[28,29]
Other vaccination impact assumptions				
% Vaccine serotype coverage	100	57	100	[8,40]
% Relative coverage[a]	90	80	100	Assumption
% Decrease in dose efficacy per yr[b]	4.8	0.0	5.0	[28]
% Contribution of herd effect in <5 yr[c]	100	100	110	Assumption

[a] Relative coverage is the coverage in those at risk of getting the disease (i.e., effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.
[b] To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3 mo, 4–5 mo, 6–8 mo, 9–11 mo, 12–23 mo, 24–35 mo, 36–47 mo, 48–59 mo) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.
[c] Rather than endogenous modeling of transmission dynamics, the % direct protection <5 yr is multiplied by a herd effect multiplier (e.g., 110%) to give the % total protection in the cohort of interest before age 5.0 yr. This excludes any herd effect in individuals aged 5 yr+ and is therefore very conservative.

Table 6
Discounted health benefits (discounted at 3% per year) for 10 cohorts vaccinated over the 2014–2023 period.

	No vaccine (status quo)	RV5 With vaccine	Averted
Total cases <5 yr (×1000)	64,465	29,335	35,130
Rotavirus (non-severe) cases (×1000)	62,525	28,661	33,864
Rotavirus (severe) cases (×1000)	1940	674	1266
Total outpatient visits (×1000)	45,125	20,534	24,591
Rotavirus (non-severe) cases (×1000)	43,767	20,063	23,705
Rotavirus (severe) cases (×1000)	1358	472	886
Total inpatient admissions (×1000)	1746	607	1139
Rotavirus (severe) cases (×1000)	1746	607	1139
Total deaths <5 yr	408	142	266
Rotavirus (severe) cases	408	142	266
DALYs lost	138,161	61,569	76,591
Due to morbidity (YLDs)	126,073	57,370	68,703
Due to mortality (YLLs)	12,088	4200	7888

admissions (Table 7). The total vaccination cost for the 10 cohorts would be US$ 499.91 million (Table 8).

3.3. Cost-effectiveness estimates

Our final results in this section showed that rotavirus vaccine is a highly cost-effective intervention compared to no vaccination from the government perspective. The estimated cost per DALY averted was US$ 2868 from the government perspective (Iran's GDP per capita as used in the model was equal to US$ 4763). Also from the government's perspective, the estimated costs were US$ 27,844 per life-year gained, US$ 825,098 per death averted, US$ 203 per inpatient admission averted, and US$ 6 per case averted. From the society perspective, the estimated cost per DALY averted was US$ 382.

3.4. Sensitivity Analysis

The results of the deterministic sensitivity analysis showed that disease incidence, vaccine price, case fatality ratio, and vaccine efficacy were among the most important parameters that can change the ICER. As shown in Fig. 1, on the basis of the WHO threshold, from both the societal and government perspectives, the rotavirus vaccine was not cost-effective in the least favorable scenario for vaccine introduction, that is, lowest disease incidence, low vaccine efficacy (a 63.9% low and a 48.3% very low estimate), low serotype coverage, low health care utilization cost, low relative coverage of death, and highest vaccine price and system costs. In other cases, the intervention was always cost-saving, very cost-effective or cost-effective.

Table 7
Discounted economic benefits (costs are discounted at 3% per year) for 10 cohorts vaccinated over the 2014–2023 period.

	No vaccine (status quo)($)	RV5 With vaccine ($)	Averted ($)
Total gov. health service costs[a] (×1000)	453,208	172,937	280,270
Total outpatient visit costs (×1000)	148,524	67,072	81,452
Rotavirus (non-severe) cases (×1000)	139,421	63,909	75,512
Rotavirus (severe) cases (×1000)	9103	3163	5940
Total inpatient admission costs (×1000)	304,683	105,865	198,818
Rotavirus (severe) cases (×1000)	304,68	105,865	198,818
Total societal health service costs[b] (×1000)	785,841	315,221	470,619
Total outpatient visit costs (×1000)	402,083	181,881	220,202
Rotavirus (non-severe) cases (×1000)	380,177	174,270	205,907
Rotavirus (severe) cases (×1000)	21,907	7612	14,295
Total inpatient admission costs (×1000)	383,757	133,340	250,417
Rotavirus (severe) cases (×1000)	383,757	133,340	250,417

[a] Government perspective includes all bed day and disease-specific drug/diagnostic costs borne by the government at the following health providers: health center, public primary/secondary/tertiary hospital.
[b] Societal perspective includes all costs included in the government perspective. In addition, it includes all household costs incurred when visiting both government and private health providers.

4. Discussion

Based on the results of TRIVAC, rotavirus vaccination was highly cost-effective from the societal and governmental perspective. It

Table 8
Discounted cost-effectiveness of RV5 (costs and DALYs discounted at 3% per year) for 10 cohorts vaccinated over the 2014–2023 period.

	RV5 Government perspective	Societal perspective
Cost-effectiveness compared to no vaccine		
Net cost of vaccine introduction (×1000)	$219,640	$29,291
Costs of vaccine introduction (×1000)	$499,911	$499,911
Health service costs avoided (×1000)	$280,270	$470,619
DALYs averted	76,591	76,591
Due to morbidity (YLDs)	68,703	68,703
Due to mortality (YLLs)	7888	7888
US$ per DALY averted	2868	382
Cost-effectiveness threshold		
1 × GDP per capita (2013)—WHO threshold for "highly cost-effective"	$4763	$4763
3× GDP per capita (2013)—WHO threshold for "cost-effective"	$14,289	$14,289

also will be cost-saving from the government perspective at a vaccine price per dose less than US$ 5.2.

Our analysis estimated that vaccination could prevent more than 35.1 million cases of rotavirus-associated diarrhea within the study time horizon (2014–2023). A national rotavirus immunization program was estimated to prevent 65% of all rotavirus-related deaths. The economic burden of rotavirus-associated hospitalizations and outpatient visits among children aged less than 5 years in Iran during the study time horizon was calculated to be US$ 785.84 million from the societal perspective. About 60% (US$ 470.61 million) of this cost could be prevented through vaccination.

Results of previous studies have shown that rotavirus vaccination would be a cost-effective public health intervention in various developing countries. For example, in Kenya, Rotarix® and RotaTeq® have a cost-effectiveness ratio of US$ 142 and 288 per DALY averted from a societal perspective [41]. In Vietnam, universal vaccination of infants at a cost of US$ 7.26 or less per vaccine dose would be a cost-effective public health intervention [42]. In Thailand, as part of the national immunization program, the rotavirus vaccine would be cost-effective at the price of US$ 6.20 per dose; at a maximum vaccine price of US$ 6.20–10.50 per dose, the cost-effectiveness ratio is approximately US$ 185–759 per DALY averted [43]. In Uzbekistan, rotavirus vaccination could be cost-effective with vaccine prices in the range of US$ 2–25 per child [44].

One study evaluated the cost-effectiveness of introducing rotavirus vaccination in GAVI-eligible countries [9]. The results showed that in a baseline scenario with an initial vaccine price of US$ 7 per dose for a 2-dose vaccine, and with a gradual decrease in vaccine price over time, vaccination was highly cost-effective in all the GAVI-eligible countries, based on their GDP-based thresholds. In addition, a national rotavirus immunization program for Brazilian children would be cost-saving with a price less than US$ 2.2 per dose [45].

The estimated ICER in our study is higher than in most of the other developing countries. This can be explained partially by a low case fatality ratio of rotavirus in Iran, a lower level of health care utilization in terms of frequency and intensity, and a higher vaccine price.

Although a rotavirus vaccine program has the potential to be cost-effective, cost-effectiveness results should be interpreted with consideration to country-specific comparators for improving the health of children. For instance, there are other completed or undergoing studies in Iran on the cost-effectiveness of vaccines against *Haemophilus Influenzae* type b [46], pneumococcal diseases, influenza virus, and acellular pertussis. All these vaccines could possibly be introduced to the national program of immunization [27]. Sustainability is another important issue for introducing a new vaccine, and it can be influenced by such factors as vaccine price,

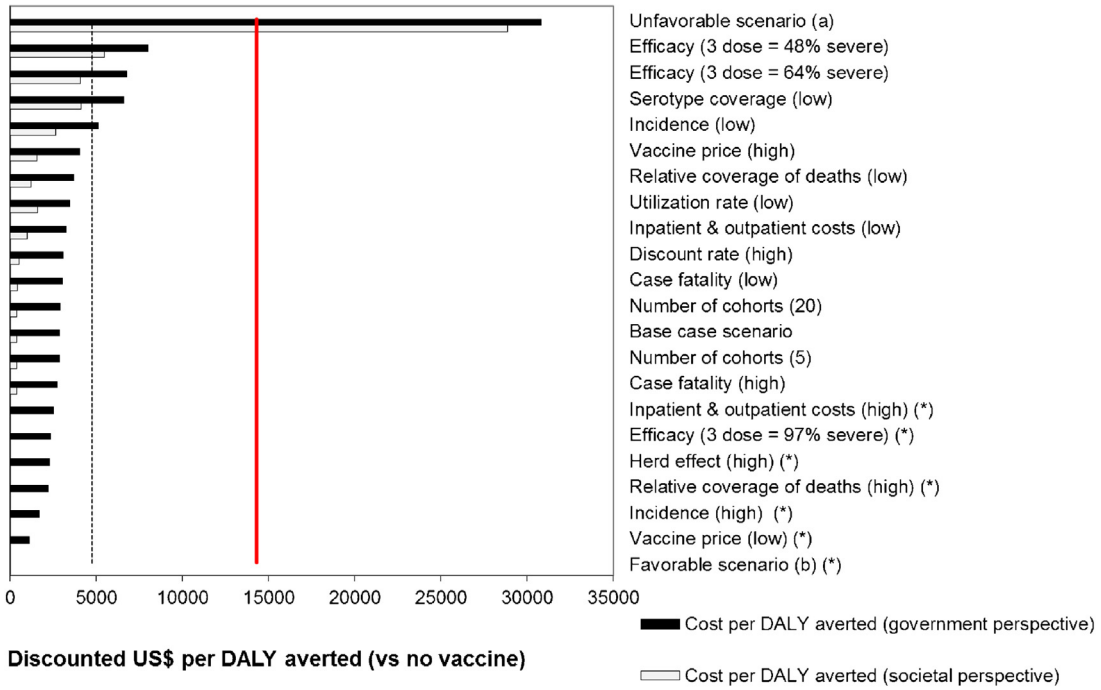

Fig. 1. *US$ per DALY averted for base case RV5 scenario and alternative "what-if" scenarios: government perspective and societal perspective.*(1) [a] Unfavorable scenario = low disease incidence, low serotype coverage, low death coverage, low vaccine efficacy (64%), low health care utilization cost, low relative coverage of death, and high vaccine price and system cost. (2) [b] Favorable scenario = high disease incidence, high serotype coverage, high death coverage, high vaccine efficacy, high health care utilization cost, high relative coverage of death, and low vaccine price and system cost. (*) Scenario is cost-saving from a societal perspective, i.e., the health service costs avoided (by both the government and households) exceeds the cost of introducing the vaccine.

availability of financial resources in the health system, and country potential for technology transfer.

Using local cost and epidemiological data in our analysis is a good base for local health policy-making. However, there are some limitations in the study. We made several assumptions that could affect the results of the analysis. We estimated the case fatality ratio in severe cases at 0.02%, based on national death registries and expert opinion. This figure is lower than the WHO estimation [47], but it seems to be the closest to the country reality. Our estimation for incidence of RVGE was higher than estimates of Bilcke et al. (0.31 per person-year), however we preferred to use our estimate which is based on the local data from Iran and is also more compatible with Walker et al. systematic review on incidence of diarrhea in low and middle income countries [48,49]. We obtained vaccine efficacy data from the international literature, using estimates from Latin American and Asian countries with fairly high VE rates, so the efficacy might be different in Iranian patients. However, we used data from the same WHO mortality stratum, B. Moreover, vaccine effectiveness may be lower than trial efficacy because of suboptimal vaccine storage and administration and differences in disease epidemiology. We assumed a 90% relative coverage of deaths because of their potential concentration among unvaccinated children; however, since the expected vaccine coverage is very high, this is a pessimistic assumption and real efficacy of vaccine for preventing deaths should be higher. We assumed vaccine coverage based on that for other vaccines, which may not be an accurate estimation of coverage for the rotavirus vaccine. However, the majority of parameters with uncertain values could be tested in the scenario analysis (using high and low values). That testing showed that the results of the base-case scenario were robust, and with most scenarios resulting in the vaccine being highly cost-effective or cost-effective. The exception was the least favorable scenario. We ran the model again after using a very low vaccine efficacy of 48.3% for full dose based on the overall Vietnam and Bangladesh estimates from the Asian study [29]. This led to an intervention that was still cost-effective from the government and societal perspective. Also, uncertainties about the VE of diverse genotypes of rotavirus have not been seen in the literature [50,51].

We did not have access to the proportion of episodes of non-severe diarrhea that are related to Rotavirus in the community setting. We used the proportion estimated through outpatient cases for this purpose that might not be an exact assumption. We did not consider the extra cost of visits by *behvarz* and health post officer personnel, who are non-physician care providers (applicable in 8.4% of cases of diarrhea where health care is sought). This was mainly because of the type of their contract (fixed monthly salary) and available unused capacities in most parts of the health network. We think that considering this opportunity cost would have a small effect on the cost-effectiveness profile in favor of doing vaccination.

Finally, it is evident that when allocating scarce community resources, the adopted perspective should reach beyond that of the provider (the health care system), which can be too restrictive. This study considered two different perspectives (societal and government) but only direct medical cost was included in the cost estimation. Such other costs as productivity loss of the parents, deceased cases due to diarrhea, and direct non-medical costs could change our results in the base-case analysis. However, we are confident that our results are conservative and that the vaccine cost-effectiveness profile in Iran probably would be better if we included those costs.

5. Conclusion

Due to the high morbidity and incidence of rotavirus diarrhea, rotavirus vaccine should be included in the Expanded Program on Immunization in Iran in the future. This cost-effectiveness analysis demonstrated that introducing rotavirus vaccine into the program could be highly cost-effective from the government and societal perspective.

Competing interest

The authors have declared that no competing interests exist.

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